

Strong family history and cigarette smoking as risk factors of coronary artery disease in young adults*

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SUMMARY This study is based on 435 consecutive patients age 50 or less who had coronary arteriography. There were 335 patients with coronary artery disease and 100 with normal coronary arteries. Risk factors reviewed were "packet-years" of cigarette smoking, family history of coronary disease in first-degree relatives 50 years of age or less, age- and sex-corrected serum cholesterol and triglycerides, hypertension, and diabetes. By univariate analysis, each risk factor except hypertension and diabetes was significantly more frequent in patients with coronary disease than in those without. By multivariate analysis of all risk factors in patients with and without coronary disease, the male or female patient with coronary disease could best be identified by the strong family history, cigarette smoking history, and age- and sex-corrected serum cholesterol. The percentage of patients with coronary disease when the three risk factors were present was 95%, two factors present 88%, one factor present 67%, none of the three 25%, strong family history alone 90%, smoking alone 66%, and serum cholesterol >80th centile alone 52%.

Coronary atherosclerotic disease starts at a young age and takes many years to progress into the symptomatic stage.¹ By the time the first symptom appears, the disease is advanced to two- or three-vessel involvement in most patients,² and indeed sudden death may be the first symptom in nearly one-third of patients.³ It is imperative that these patients be identified at a young age before the first symptom appears, for it is at the early stages of the disease, rather than in the later symptomatic stages, that intervention to prevent progression of disease and death is most likely to be successful. Furthermore, when the disease appears at a young age, it might be more rapidly progressive unless interventions are made. Improvement in identification of the large majority of young persons in the general population at high risk of developing coronary disease by noninvasive methods is needed. As a first step in approaching this problem we have reviewed the risk factors in 435 patients 50 years of age or younger who had coronary arteriography.

Patients and methods

Patients selected for study included consecutive Caucasian patients of 50 years of age or less who had

coronary arteriography because of typical or atypical chest pain from 1 July 1975 to 30 June 1977. The patients were divided into two groups: (1) 335 patients with coronary artery disease (median and mean ages 46 and 45 years respectively, 88% men) who had at least one coronary artery stenosed >50% in luminal diameter (138 or 41% had previous myocardial infarction) and (2) 100 patients (median and mean ages 44 and 43 years respectively, 58% men) who had angiographically normal coronary arteries, no previous myocardial infarction by history or electrocardiographic criteria, and no clinical evidence of peripheral arteriosclerosis obliterans as judged by normal arterial pulses and absence of claudication and bruits. Patients with coronary lesions <50% in luminal diameter, and associated valvular, congenital, or cardiomyopathic heart disease were excluded.

RISK FACTORS

The following risk factors were considered.

(1) Cigarette smoking

The number of "packet-years" (number of packs (20 cigarettes per pack) per day times number of years smoked) of smoking was determined from the patient as previously described and along with the current smoking status (smoking within a week before coro-

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nary arteriography). In the text we will use number of years of smoking to mean the numbers of packet-years of smoking.

(2) Family history

We only considered a strong family history of coronary disease (myocardial infarction, sudden death, exertional angina, or disease documented by coronary angiography) in first-degree relatives who were age 50 years and under as previously described.⁴

(3) Hyperlipidaemia (at the time of admission for coronary arteriography)

Hypercholesterolaemia and hypertriglyceridaemia were analysed as previously described⁴ and defined as at or above the 95th or 80th centile* for a patient's age and sex, and for discriminant function analysis as the age- and sex-corrected serum cholesterol and triglyceride relative deviate.

(4) Systemic hypertension

This was taken as positive if the diagnosis ($>160/95$ mmHg) had been made before coronary arteriography (and patients were subsequently given antihypertensive medication) or if at the evaluation for coronary arteriography the blood pressure was $\geq 160/95$ mmHg on three occasions.

(5) Diabetes mellitus

This was defined as two fasting plasma glucose values ≥ 6.6 mmol/l (≥ 120 mg/dl) normal ≤ 5.5 mmol/l (normal ≤ 100 mg/dl) or insulin dependence.

CORONARY ARTERIOGRAPHY

Selective coronary cineangiography was performed with and without cranial angulation and as previously described.⁵ Patients with a maximal coronary artery stenosis $<50\%$ (22 patients) were excluded from the study to make the division between coronary disease and normal coronary arteries as definite as possible.

STATISTICS

Significance of univariate analysis of risk factors was tested by Student's *t* test or χ^2 . Stepwise linear discriminate function analysis was carried out according to the RMD P7M computer program of the Health Sciences Computing Facility, University of California at Los Angeles.

Results

PREVALENCE OF RISK FACTORS

The Figure shows the percentage of patients with each risk factor for those with and without coronary artery disease. Each risk factor except hypertension and

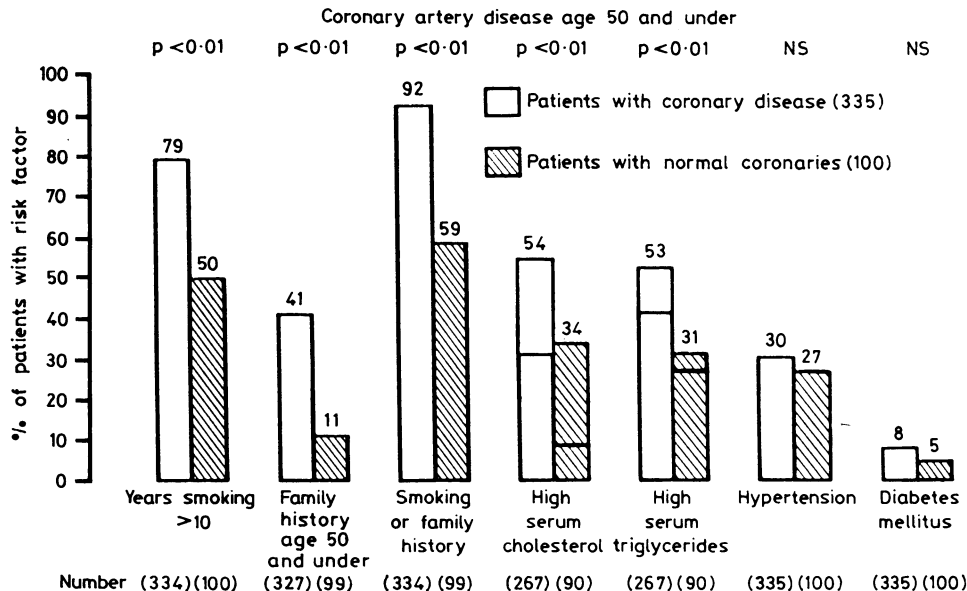


Fig. Univariate analysis of risk factors in young patients with coronary artery disease and those with normal coronary arteries. Serum cholesterol and serum triglycerides were taken at ≥ 80 th centile for age and sex (top of bar) and 95th centile (solid line in bar). Not shown is current smoking status for coronary disease (26%) and normal coronary (22%) patients. Each risk factor except diabetes, hypertension, and current smoking status was significantly ($p < 0.01$) more frequent in patients with coronary disease than in those without. Number of patients in each risk factor subgroup is shown below each bar. Patients in whom a risk factor was unknown were excluded from analysis: smoking 1, family history 8, cholesterol and triglycerides 68 (coronary disease), and 10 (normal).

*Age-sex specific centiles were established by our laboratory on the basis of 458 carefully screened healthy adults. At age 45 the 80th centiles (in mg/100 ml) for cholesterol were 250 for men and 235 for women, and the 95th centiles were 285 in men and 267 in women. For triglycerides the 95th centiles at age 45 were 195 in men and 125 in women.

diabetes mellitus was present in a significantly ($p < 0.01$) higher percentage in the patients with coronary artery disease. Cigarette smoking was the single most frequent risk factor in patients with coronary disease, being present in 79% of the patients. Family history of coronary artery disease at a young age was found in 41% of patients with coronary artery disease and only 11% of normal patients. A cholesterol level at or above the 95th centile was found in 31% of patients with coronary disease and 9% of patients with normal coronary arteries. A triglyceride level at or above the 95th centile was found in 41% of patients with coronary disease but also in 27% of normal patients. We also looked at the percentage of patients with cholesterol and triglyceride levels at or above the 50th and the 80th centiles for age and sex (Fig. and Table 1). The presence of a history of cigarette smoking or a positive family history (or both) was found in 92% of patients with coronary disease and 59% of patients with normal coronary arteries (Fig.).

Table 1 Risk factor prevalence in patients with and without coronary disease at different cut points in three of the continuous variables: the patients are those in whom all risk factors were available for analysis

	Males		Females		Total	
	CAD	No CAD	CAD	No CAD	CAD	No CAD
n=351	232	53	30	36	262	89
	%	%	%	%	%	%
Age <40	16	40	10	17	15	27
Family history	41	11	37	8	40	10
Packet-years						
0	16	21	20	69	17	40
≥10	79	68	73	28	79	52
≥30	49	32	40	8	48	22
Cholesterol						
>P ₅₀	81	58	87	58	82	58
>P ₈₀	53	34	60	33	54	34
<P ₉₅	28	6	47	11	30	8
Triglyceride						
>P ₅₀	86	66	77	83	85	73
>P ₈₀	51	30	70	33	53	31
>P ₉₅	39	25	57	31	41	27
Hypertensive	30	40	10	17	28	30

PREDICTIVE VALUE OF RISK FACTORS

Linear discriminant analysis

Stepwise linear discriminant function analysis in the 351 patients in whom all the risk factors were available for analysis (family history, number of packet-years of cigarette smoking, current smoking status, age- and sex-corrected cholesterol and triglyceride levels, hypertension, systolic blood pressure, diastolic blood pressure, and diabetes mellitus) showed that the young patient with coronary artery disease could best be identified by cigarette smoking, family his-

Table 2 Stepwise linear discrimination between those with and without coronary disease

	(N=351)		
	Men	Women	Total
Selected* by linear discriminant function	Chol Age Fam. Hx. Packet-years+	Packet-years Chol Fam. Hx.	Sex Chol Fam. Hx. Packet-years Age

N, number of patients.

*Using F to enter ≥ 4 ($p < 0.05$) when age is dropped.

Fam. Hx., strong family history; Packet-years, number of packet-years of cigarette smoking; Chol, age- and sex-corrected serum cholesterol relative deviate.

tory, cholesterol, sex, and age. Table 2 summarises the results of stepwise linear discrimination between those with and those without coronary artery disease for men, women, and the total group and lists the variables selected in order of their discriminating power. Sex-corrected cholesterol, strong family history, and packet-years of cigarette smoking were selected by linear discriminant function in both sexes. Age was not selected in women probably because of the smaller age spread (see Table 1).

Univariate analysis

Table 3 describes the coronary disease prevalence in eight subgroups defined in terms of strong family history, cholesterol level above the 80th centile for age and sex, and 10 years or more of cigarette smoking in the 351 patients (262 with and 89 without coronary disease) for whom data on all three of these risk factors were available. When none of these risk factors are present 25% of patients have coronary disease, with one of these factors 67% have coronary disease, with two of these factors 88% have disease, and the increase is small (88% to 95%) with a third risk factor.

Table 3 Coronary disease prevalence in subgroups defined by family history, cigarette smoking, and cholesterol risk factors

Family history	Cholesterol >P ₈₀	≥10	N	% CAD
+	+	+	42	95
+	—	+	32	97
+	+	—	19	79
—	+	+	83	87
+	—	—	21	90
—	—	+	95	66
—	+	—	27	52
—	—	—	32	25
				351

N, number of patients; CAD, coronary artery disease.

Strong family history is the single risk factor that is associated with the greatest prevalence of coronary disease (90%), followed by ≥ 10 years cigarette smoking (66%), and cholesterol level above the 80th centile (52%). These above results would change if the cut points for centile of cholesterol and number of years of cigarette smoking were changed. Table 1 describes the results in the same 351 patients included in Table 3 without regard to subgroup analysis but at different cut points for centile cholesterol and triglycerides and number of years of smoking.

Discussion

This study clearly shows the association between the strong family history, cigarette smoking, and age- and sex-corrected cholesterol risk factors and the presence of coronary disease in young patients having coronary angiography. These are factors of recognised importance in the development of coronary artery disease in the general population, but the strong family history risk factor (in first degree relatives at age 50 and under) is not widely recognised and has not frequently been looked for in large prospective epidemiological studies. While it is not surprising that the association penetrates to this angiographic subgroup, the strength of the association may have been materially altered by the selection process of patients for coronary angiography. A safe, noninvasive measure of the degree of coronary stenosis comparable in accuracy to angiography could determine the strength of this association in the general population, but such a noninvasive method is not yet available.

Studies aimed at risk factor prediction of the presence or absence of coronary disease which involve individuals who are candidates for coronary arteriography have the advantage of eliminating the misclassification which results from errors of clinical diagnosis.⁶ Individuals who have had coronary arteriography, however, do not necessarily represent the general population since, on the one hand, those with coronary disease and no symptoms of coronary disease are underrepresented, and those who die at the initial event are missing. Though the subgroup with normal coronary arteries is missing those with no symptoms, this subgroup has been shown, when restudied after 12 to 104 months, to have a benign prognosis⁷ and normal coronary arteries.^{8, 9} This group was also free of clinical peripheral atherosclerotic disease.

It is difficult to establish the precise order of importance of the three major risk factors. For a single risk factor, strong family history is associated with the largest increase in coronary disease prevalence, and years of smoking is next (Table 3). By stepwise linear discrimination all three are significant

in identifying the coronary patient, but cholesterol ranks ahead of the other two in men and in the total group while years of smoking ranks first in women (Table 2). In univariate analysis the three risk factors are all highly significant. For example, using strong family history, the difference in the percent positive gives $\chi^2_1 = 27$; cigarette smoking ≥ 30 years gives $\chi^2_1 = 18$, and cholesterol above the 90th centile for age and sex also gives $\chi^2_1 = 18$. The method of statistical observation and the cutoff point used for a continuous variable may change the order of apparent importance. We found from practical and clinical standpoints that it is uncommon to find a patient 50 years of age or younger with angiographically proven coronary artery disease who does not have a cigarette smoking history or a positive family history of coronary artery disease at a young age. It is also uncommon to find angiographically normal coronary arteries in a young person who has both of the latter risk factors or all three of these risk factors ($\leq 5\%$) as noted in Table 3.

Cigarette smoking is a well-recognised primary risk factor^{10, 11} in men¹² and women¹³ and a recently recognised cause of secondary complications in patients with known coronary artery disease who continue to smoke, compared with former smokers or nonsmokers.^{11, 13} We found that a history of 10 years or more of cigarette smoking increases the risk of having coronary artery disease whether or not the patient is currently smoking. Thus, in taking the history it is important to determine a quantitative estimate of previous cigarette smoking since only a small number of patients may be currently smoking. We observed only 26% of patients with coronary disease and 22% of patients with normal coronary arteries to be currently smoking. The mechanism whereby smoking contributes to the development and complications of coronary artery disease is unknown but is discussed by us elsewhere.⁴ Unfortunately, there is an alarming trend toward increased smoking in women and young people,¹⁴ and, therefore, better methods leading to prevention and cessation of smoking are needed.

It is important to note the strength of the family history risk factor in a patient's history since the occurrence at a young age appears to be associated with coronary disease in other young family members who present with symptoms of possible coronary disease. It is of interest that clinical manifestations of coronary disease show similarities within sibships such as cardiac deaths being most common in sibs of the fatal infarction probands.¹⁵ The younger the age at diagnosis the greater the risk of premature coronary disease in other first-degree relatives.¹⁶ Slack and Evans¹⁷ found that the risk of coronary death under age 55 is 5.2 times that of the general population if a male first-degree relative has died from coronary

disease under age 55, and 2.8 times if the relative is a woman under age 65. These increases in risk are about twice that experienced by middle-aged men with serum cholesterol over 7.8 mmol/l (300 mg/dl) or diastolic blood pressure over 105 mmHg.¹⁸ Since the strong family history risk factor is dependent on sibship size and birth order of the subject in relation to sibs, the absence of sibs or the subject being oldest among sibs, would probably lead to underestimation of the frequency of this risk factor. The genetic factor that contributes to the development and progression of coronary artery disease is unknown, can only be speculated upon, and is discussed by us elsewhere.⁴ Unlike studies from the Finnish population¹⁹ we found that those with and without a positive family history did not differ significantly in any of the other risk factors. We found the cholesterol and triglyceride distributions for patients with a positive and those with a negative family history of coronary artery disease were not significantly different. In addition, in the subgroup of patients with both strong family history and cigarette smoking regardless of serum cholesterol, 96% (71/74) had coronary artery disease. It is also striking that 90% of patients with the strong family history risk factor alone had coronary disease. Asymptomatic young adults with the strong family and/or the cigarette smoking risk factors have a high incidence of a shortened ⁵¹Cr platelet survival half-life suggesting enhanced platelet-arterial wall interaction⁴ and the possibility that these individuals with risk factors and/or shortened ⁵¹Cr platelet survival half-life may have subclinical atherosclerotic disease and might be good candidates for an early intervention trial in the "prevention" of coronary artery disease.

Hypercholesterolaemia is a well-documented primary risk factor^{10, 11} and a recently documented secondary risk factor²⁰ of coronary artery disease. Lowering of serum cholesterol may retard angiographic progression of coronary artery disease²¹ and reduce mortality from coronary artery disease.²² The increase in coronary artery disease with increasing serum lipid concentrations holds over the entire range, without any critical serum level to separate risk from non-risk groups.²³ The association was stronger with cholesterol than with triglyceride. Premature or accelerated atherosclerosis occurs in patients who have hyperlipoproteinaemia, but hyperlipoproteinaemia, as we also observed, is neither necessary nor sufficient for atherosclerosis.²⁴ Because the incidence of coronary artery disease and the levels of serum cholesterol in presumably healthy persons in the United States are higher than those in most countries of the world (including countries where smoking is prevalent), cholesterol may play a permissive role in the development of atherosclerosis. For example, in Japan, where smoking is very prevalent, the levels of serum chole-

sterol and the incidence of coronary artery disease are very low.²⁵

Hypertension is both a primary¹⁰ and a secondary¹¹ risk factor. In the two groups of young patients having angiography, we found no difference in the proportion with hypertension. It is possible that if we had been able to integrate the level of increase over time, an association might have been found. In addition, some of those with the longest duration of high levels of blood pressure might have been lost by death at the initial manifestation of coronary artery disease (sudden death or fatal myocardial infarction).

Although these risk factors identify groups at high risk for having coronary artery disease at a young age, they are not as specific as coronary arteriography for identification of coronary disease. Not all risk factors, however, have necessarily been identified. The angiographic groups offer an opportunity for intensive studies to identify new risk factors. Since platelets appear to play a role in the development of atherosclerotic disease, we evaluated the relation between the risk factors found here and platelet consumption as assessed by ⁵¹Cr platelet survival half-life.⁴ We are also following medically treated coronary disease patients in a prospective, randomised, double-blind, platelet inhibitor drug trial, and will be able to see if the strong family history risk factor or platelet survival half-life are secondary risk factors in the angiographic progression of coronary artery disease.²⁶

Thus, the strong family history is an independent risk factor not associated with a clustering of other risk factors. It helps identify young patients at risk of having coronary disease along with the cigarette smoking history and serum cholesterol and appears to be associated with enhanced platelet-arterial wall interaction.⁴

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